Eleanor F. Barbo
Senior Director, Regulatory Affairs

Whitehall-Robins Healthcare
Five Giralda Farms
Madison, NJ 07940
Telephone (973) 660-5751
Fax (973) 660-6048
E-mail address: barboe@ahp.com

WHITEHALL ROBINS

November 8, 1999

Docket No. 97D-0433: Draft Guidance for Industry on Average, Population, and Individual Approaches To Establishing Bioequivalence

Dockets Management Branch (HFD-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Sir or Madam:

Comments are being submitted by Whitehall-Robins Healthcare ("Whitehall-Robins"), a Division of American Home Products Corporation, to Docket No. 97D-0433 in response to the Draft Guidance, entitled "Average, Population, and Individual Approaches To Establishing Bioequivalence", as referenced in the Federal Register of September 8, 1999 (Vol. 64, No. 173, page 48842).

We appreciate the additional opportunity to comment on this draft guidance which has incorporated some of our comments based on the previous preliminary version. We do, however, still have several serious concerns that are discussed in detail in the Attachment to this letter. With these further clarifications and modifications, this guidance would be an improvement over current procedures for bioequivalence testing.

We commend the Agency in their ongoing efforts in this current draft to establish meaningful and useful criterion for declaring new formulations of drugs bioequivalent to reference formulations. Additionally, we welcome the opportunity to continue participating in the evolution of the guidelines for *In Vivo* bioequivalence studies.

We anticipate that you will address the concerns as noted in our attached comments and that you will develop a revised draft for industry comment before finalizing this guidance. If you have any questions, please contact me at 973-660-5751.

Sincerely yours,

WHITEHALL-ROBINS HEALTHCARE

Eleanor F. Barbo
Senior Director, Regulatory Affairs

Enclosure

97D-0433

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Comments on "Draft Guidance for Industry on Average, Population, and Individual Approaches to Establishing Bioequivalence" (Docket No 97D-0433)

Thank you for providing Whitehall-Robins Healthcare an opportunity to respond to this draft guidance. The guidance has incorporated recent statistical thinking and, with modifications, represents a potential improvement over current procedures for bioequivalence testing. We do, however, have some serious concerns that we would like to share with you in the hope that these can be addressed in the final rules.

This guidance implies that establishment of bioequivalence based purely on average bioavailability has the potential of approving markedly inferior formulations while denying approvability to formulations that represent true improvements. It recognizes that the comparative variability of the test to reference formulation may be a crucial factor and that, in the context of switchability, subject-by-formulation interactions may be critical components that require due consideration. The proposed criteria represent a good starting point for incorporation of these factors; however, as currently proposed, we believe they have significant shortcomings.

- Lack of a clinical imperative for new bioequivalence criteria: While it is true that average bioequivalence (ABE) criteria take into account neither the relative variabilities of the formulations nor the subject-by-treatment interaction, has this shortcoming led to safety or efficacy problems in formulations approved under ABE? Such data, if any, should be referenced in the rationale for the new guidance. The replicated crossover design that is required for individual bioequivalence is a more difficult design to administer and will lead to higher dropout rates. In the absence of a clear clinical rationale, imposing upon sponsors the extra complexity and resulting problems of this design is unjustified.

- Clarification on when IBE, PBE, ABE or a combination would be required: The guidance indicates that population bioequivalence (PBE) and individual bioequivalence (IBE) "supplement" ABE. Does this mean that *either* PBE (or IBE) or ABE criteria is required to be satisfied, or that *both* need to be satisfied, or that for some drugs ABE is required while for others PBE (or IBE) is required? Besides clarifying this issue, the guidance should also provide further clarification in helping sponsors determine whether PBE or IBE is required for post-approval changes in the formulation and manufacture of a drug product.

- Concerns about proposed aggregate rules for PBE and IBE: No rationale is provided for the 0.2 allowance for differences in variances between the formulations. More importantly, bioequivalence can be too easily declared in some cases. For example, under the proposed IBE rule, a test formulation with the same variance as the reference formulation can be declared bioequivalent to it when the average bioavailabilities differ by almost 40% and even more so for highly-variable drugs.

- Clarification of guidance in case of multiple test formulations: The guidance implies that in a single trial only one test formulation can be compared to a reference formulation. There is an occasional need to compare multiple formulations. Sometimes, a sponsor needs to test whether there are food effects for a new formulation. In both these cases, the sponsor would need to carry out multiple trials. This extra burden is in addition to the extra burden imposed by the increased complexity of the replicated design. The final guidance should provide direction on how sponsors should handle these situations.

- Mandatory inclusion of elderly subjects in bioequivalence trials: Another extra burden imposed upon sponsors is the mandatory inclusion of elderly subjects. These subjects are typically harder to recruit for routine bioequivalence studies. In the absence of compelling evidence or *a priori* data demonstrating lack of bioequivalence between younger and older subjects with the reference formulation, this mandatory requirement seems unjustified.

- Formulas for the 95% confidence intervals: The formulas for providing the 95% upper confidence bounds for PBE and IBE are not familiar. They should either be justified or a reference should be provided.

We understand that the FDA is planning on evaluating the results of ABE to PBE/IBE testing over a two-year trial period. We recommend criteria and endpoints for comparing the different approaches and for declaring whether the new rules provide a real benefit be established and publicly shared so that comments can be provided prior to its implementation.

We congratulate the Agency for attempting to create more meaningful and useful criteria for declaring new formulations of drugs bioequivalent to reference formulations. The criteria and methodologies proposed in this draft guidance document, although seriously flawed, have strong merits as well. We would encourage the Agency to address the concerns raised here and issue a revised draft before implementing this guidance.

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